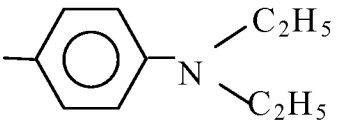
CURRENT LISTING OF THE CLAIMS

1 (Currently amended). A specificity-determining substrate that reversibly forms a complex with a protein molecule in a homogenous fashion, suitable for proteomic separations, wherein the specificity-determining substrate comprises a specificity-determining ligand bound to a support, ~~wherein optionally the substrate further comprises a spacer bound between the ligand and the support,~~ wherein the spatial separation between adjacent ligand groups is greater than a predetermined minimum distance, wherein the predetermined minimum distance is greater than about 5 Å, and provided that the substrate is other than a crosslinked chitosan bearing a diethylamino or diethylaminoethyl ligand.

2 (Original). The substrate described in claim 1 wherein the specificity-determining ligand is chosen from the group consisting of a monosaccharide, a disaccharide, a trisaccharide, an oligosaccharide, $CH_3(CH_2)_3NHCH_2CH_2O—$, $CH_3(CH_2)_3N(—)CH_2CH_2OH$, $(CH_3)_3CNH—$, $(CH_3)_3CN(—)CH_2CH_2OH$, $(CH_3)_3CNHCH_2CH_2O—$, $[(CH_3)_2NCH_2]_3C_6H_2O—$, $[(CH_3)_2NCH_2]_3C_6H_2O—$, $CH_3(CH_2)_7NH—$, $[(CH_3)_2CH]_2N—$, $C_6H_{13}NH—$, $(C_2H_5)_2N—$, $C_6H_5CH_2NH—$, 1,2,4–benzenetricarboxyl-5-carbonyl, trimethylacetyl, benzoyl, $HOOC(CH_2)_2CO—$, $HOOCC[(C_6H_5)]_2CO—$,



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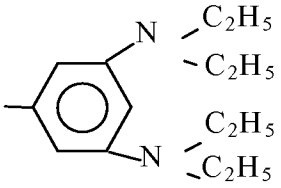

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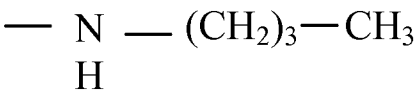

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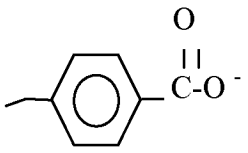

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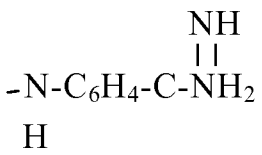
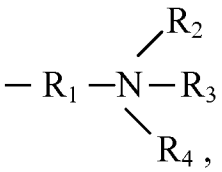
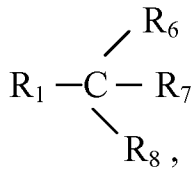


, and .

3 (Original). The substrate described in claim 1 wherein the specificity-determining ligand comprises





- R_1-O-R_5 ,

- R_1-COOH or R_1-COO^- ,

- R_1-$OSO_3^=$,

or

- R_1-$OPO_3^=$ or -R_1-OPO_3H^- or -R_1-OPO_3H_2,

wherein R_1 is chosen from the group consisting of a normal or branched aliphatic moiety, a cycloalkyl moiety, an aromatic moiety, an aralkyl moiety, an aliphatic-aliphatic ether, an aliphatic-aromatic ether, an aliphatic moiety having a secondary or tertiary alcohol, a phenolic moiety, an aliphatic moiety having a secondary or tertiary amine, an aniline moiety, an aliphatic carboxyl, sulfate, sulfonate, or phosphate ester, an aromatic carboxyl, sulfate, sulfonate or phosphate ester, and an aromatic heterocycle;

and wherein R_2, R_3, R_4, R_5, R_6, R_7, and R_8, are independently chosen from the group consisting of hydrogen, a normal or branched aliphatic radical, a cycloalkyl radical, an aromatic radical, an aralkyl radical, an aliphatic-aliphatic ether, an aliphatic-aromatic ether, an aliphatic radical having a primary, secondary or tertiary alcohol, a phenolic radical, an aliphatic radical having a primary, secondary or tertiary amine, an aniline radical, an aliphatic carboxylate, sulfate, sulfonate, or phosphate group, an aromatic carboxylate, sulfate, sulfonate or phosphate group, and an aromatic heterocycle.

4 (Currently amended). The substrate described in claim 1 wherein ~~a spacer is~~

~~—CH(OH)CH$_2$CH$_2$O(CH$_2$)$_m$OCH$_2$CH$_2$CH(OH)—,~~

~~—CH(OH)CH$_2$CH$_2$O(CH$_2$)$_m$OCH$_2$CH$_2$CH(OH)NH—,~~

~~—CH(OH)CH$_2$CH$_2$O(C$_m$H$_{2m-2}$)OCH$_2$CH$_2$CH(OH)—, or~~

~~—CH(OH)CH$_2$CH$_2$O(C$_m$H$_{2m-2}$)OCH$_2$CH$_2$CH(OH)NH—, where *m* is an integer between 2 and 10~~ the substrate further comprises a spacer bound between the ligand and the support.

5 (Original). The substrate described in claim 1 wherein the support is chosen from the group consisting of a glass surface, a silica surface, a ceramic surface, a plastic surface, a resin particle, a bead, a gel, a polyelectrolyte, and a hydrogel.

6 (Original). The substrate described in claim 5 wherein the support is other than a surface and wherein the solids content of the support when equilibrated with an ambient fluid is less than a predetermined maximum content.

7 (Original). The specificity-determining substrate described in claim 6 wherein the solids content of the support is less than about 8% w/v.

8 (Original). The substrate described in claim 1wherein the support comprises a polysaccharide.

9 (Original). The substrate described in claim 1wherein the support comprises chitosan.

10 (Currently amended). A complex comprising a specificity-determining substrate described in claim 1 and a reversibly bound protein molecule.

11 (Original). A complex comprising a specificity-determining substrate described in claim 2 and a protein molecule.

12 (Original). A complex comprising a specificity-determining substrate described in claim 3 and a protein molecule.

13 (Original). A complex comprising a specificity-determining substrate described in claim 4 and a protein molecule.

14 (Original). The complex described in claim 10 wherein the support is chosen from the group consisting of a glass surface, a silica surface, a ceramic surface, a plastic surface, a resin particle, a bead, a gel, a polyelectrolyte, and a hydrogel.

15 (Original). The complex described in claim 14 wherein the support is other than a surface and wherein the solids content of the support when equilibrated with an ambient fluid is less than a predetermined maximum content.

16 (Original). The complex described in claim 15 wherein the solids content of the support is less than about 8% w/v.

17 (Original). The complex described in claim 10 wherein the support comprises a polysaccharide.

18 (Original). The complex described in claim 10 wherein the support comprises chitosan.

19 (Withdrawn). An array comprising a plurality of loci wherein each locus comprises a specificity-determining substrate described in claim 1.

20 (Withdrawn). The array described in claim 19 wherein the specificity-determining ligand at a first locus differs from a specificity-determining ligand at a second locus.

21 (Withdrawn). The array described in claim 19 wherein the specificity-determining ligand at a first locus is identical to a specificity-determining ligand at a second locus.

22 (Withdrawn). An array comprising a plurality of loci wherein each locus comprises a specificity-determining substrate described in claim 2.

23 (Withdrawn). An array comprising a plurality of loci wherein each locus comprises a specificity-determining substrate described in claim 3.

24 (Withdrawn). An array comprising a plurality of loci wherein each locus comprises a specificity-determining substrate described in claim 4.

25 (Withdrawn). A method of resolving a first protein from a fluid comprising one or more species of native, biologically active protein molecules, wherein the first protein retains its native structure and its biological activity, the method comprising the steps of:

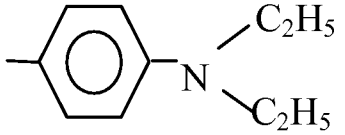
a) contacting the fluid with a specificity-determining substrate described in claim 1, thereby forming a complex comprising the first protein; and

b) separating the fluid so contacted from the complex;

thereby resolving the first protein from the fluid.

26 (Withdrawn). The method described in claim 25 wherein the fluid comprises a plurality of species of protein molecule, and the contacted and separated fluid comprises a second protein.

27 (Withdrawn). The method described in claim 25 wherein the specificity-determining ligand is chosen from the group consisting of a monosaccharide, a disaccharide, a trisaccharide, an oligosaccharide, $CH_3(CH_2)_3NHCH_2CH_2O—$, $CH_3(CH_2)_3N(—)CH_2CH_2OH$, $(CH_3)_3CNH—$, $(CH_3)_3CN(—)CH_2CH_2OH$, $(CH_3)_3CNHCH_2CH_2O—$, $[(CH_3)_2NCH_2]_3C_6H_2O—$, $[(CH_3)_2NCH_2]_3C_6H_2O—$, $CH_3(CH_2)_7NH—$, $[(CH_3)_2CH]_2N—$, $C_6H_{13}NH—$, $(C_2H_5)_2N—$, $C_6H_5CH_2NH—$, 1,2,4–benzenetricarboxyl-5-carbonyl, trimethylacetyl, benzoyl, $HOOC(CH_2)_2CO—$, $HOOCC[(C_6H_5)]_2CO—$,



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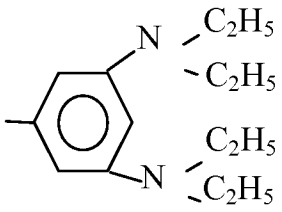

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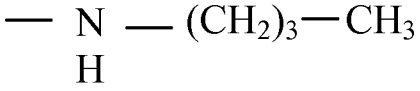

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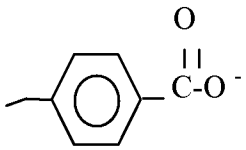

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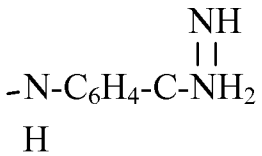

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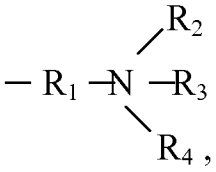
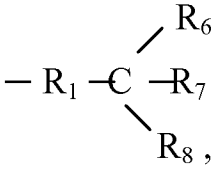
28 (Withdrawn). The method described in claim 25 wherein the specificity-determining ligand comprises



- R_1-O-R_5,

- R_1-COOH or R_1-COO^-,



- R_1-$OSO_3^=$,

or

$$- R_1\text{-}OPO_3^{=} \text{ or } -R_1\text{-}OPO_3H^{-} \text{ or } -R_1\text{-}OPO_3H_2,$$

wherein R_1 is chosen from the group consisting of a normal or branched aliphatic moiety, a cycloalkyl moiety, an aromatic moiety, an aralkyl moiety, an aliphatic-aliphatic ether, an aliphatic-aromatic ether, an aliphatic moiety having a secondary or tertiary alcohol, a phenolic moiety, an aliphatic moiety having a secondary or tertiary amine, an aniline moiety, an aliphatic carboxyl, sulfate, sulfonate, or phosphate ester, an aromatic carboxyl, sulfate, sulfonate or phosphate ester, and an aromatic heterocycle;
and wherein R_2, R_3, R_4, R_5, R_6, R_7, and R_8, are independently chosen from the group consisting of hydrogen, a normal or branched aliphatic radical, a cycloalkyl radical, an aromatic radical, an aralkyl radical, an aliphatic-aliphatic ether, an aliphatic-aromatic ether, an aliphatic radical having a primary, secondary or tertiary alcohol, a phenolic radical, an aliphatic radical having a primary, secondary or tertiary amine, an aniline radical, an aliphatic carboxylate, sulfate, sulfonate, or phosphate group, an aromatic carboxylate, sulfate, sulfonate or phosphate group, and an aromatic heterocycle.

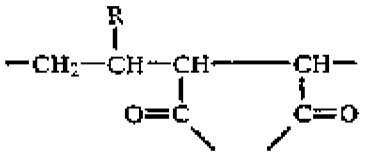
29 (Withdrawn). The method described in claim 25 wherein the support is chosen from the group consisting of a glass surface, a silica surface, a ceramic surface, a plastic surface, a resin particle, a bead, a gel, a polyelectrolyte, and a hydrogel.

30 (Withdrawn). The method described in claim 25 wherein the support comprises a polysaccharide.

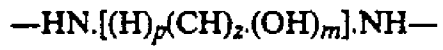
31 (Withdrawn). The method described in claim 25 wherein the support comprises chitosan.

32 (Withdrawn). The method described in claim 25 further wherein, prior to performing step a) the fluid is pretreated by a method comprising the steps of:

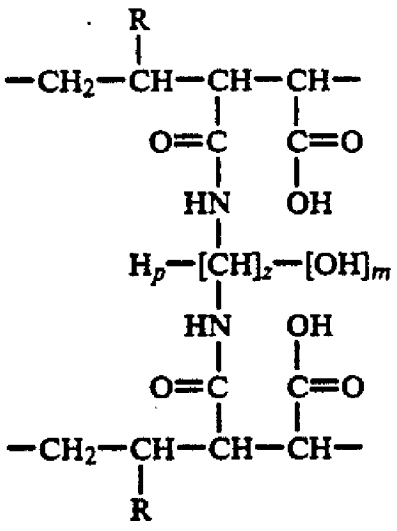
a') contacting the fluid with a hydrogel comprising a water insoluble cross-linked polyhydroxy polycarboxylic acid having at least two strands each having a strand skeleton of the formula:



wherein R is H, OCH_3, or phenyl, and one carbonyl group of at least one maleoyl moiety thereof in each strand is covalently linked to a



moiety to provide the presence therein of at least one cross linking moiety of the formula:



wherein R is hydrogen or lower alkylene or lower alkoxy of 1-4 carbon atoms, or phenyl,

z is an integer of 1-4,

p is 0 or an integer up to z-1,

m is 1 or an integer up to z,

wherein the ratio of cross-links to poly (alkylene carbonic acid) strands is between about 1 and about 200 to 2,

to provide a hydrogel phase and a first supernatant; and

a'') either

i) separating the hydrogel phase from the first supernatant and using the first supernatant as the fluid of step a) of claim 25, or

ii) separating the hydrogel phase from the first supernatant, then treating the hydrogel phase to release proteins adhering within it to provide a second supernatant comprising adhered proteins, and using the second supernatant as the fluid of step a) of claim 25.

33 (Withdrawn; currently amended). A method of purifying one or more first proteins from a fluid comprising one or more species of native, biologically active protein molecules, wherein the purified first protein retains its native structure and its biological activity, the method comprising the sequential steps of

a) contacting the fluid with a specificity-determining substrate described in claim ~~0A~~ 1, thereby forming a complex ~~described~~ comprising the one or more first proteins;

b) separating the contacted fluid from the complex; and

c) eluting the one or more first proteins from the specificity-determining substrate under conditions that retain the native structure and biological activity of the first protein; thereby providing one or more purified native, biologically active first proteins.

34 (Withdrawn). The method described in claim 33 wherein the fluid comprises a plurality of species of protein molecule, and the contacted and separated fluid comprises a second protein.

35 (Withdrawn). A method of characterizing one or more proteins in a fluid comprising one or more species of protein molecule, the method comprising the sequential steps of

a) providing a plurality of containers, wherein each container has a characteristic specificity-determining substrate described in claim 1and a characteristic set of ambient fluid conditions, and wherein ambient fluid conditions are described by one or more variables chosen from the group consisting of the temperature, the ionic strength, the fluid composition, an amount of a chaotropic agent, an amount of a detergent, an amount of an organic cosolvent, and the pH, wherein each of said ligand and said ambient fluid conditions in a first container may be the same or different from said ligand and said ambient fluid conditions in a second container;

b) contacting the fluid with the plurality of containers, thereby promoting formation of a complex comprising the one or more proteins in a first container and inhibiting formation of a complex comprising the one or more proteins in a second container;

c) identifying the promotion of complex formation in the first container and the inhibition of complex formation in the second container; and

d) identifying the ligand and ambient fluid conditions in the first container and in the second container;

thereby characterizing the one or more proteins.

36 (Withdrawn). A method of identifying one or more proteins in a sample fluid wherein the concentration of the one or more proteins in the sample fluid differs from the concentration of the one or more proteins in a reference fluid, the method comprising the sequential steps of

a) in a set of N containers, contacting the sample fluid with a specificity-determining substrate described in claim 1and an ambient fluid, wherein the ambient fluid has conditions described by one or more variables chosen from the group consisting of the temperature, the ionic strength, the fluid composition, an amount of a chaotropic agent, an amount of a detergent, an amount of an organic cosolvent, and the pH, wherein each container is characterized by a particular specificity-determining substrate and a particular fluid condition, the particular substrate and particular fluid conditions potentially promoting formation of a complex comprising the one or more proteins;

b) determining the amount and/or species of protein molecules complexed with the substrate in each container of the sample fluid set;

c) comparing the amount and/or species of protein molecules complexed with the substrate in each container of the sample set with the amount and/or species of protein molecules complexed with the substrate obtained by contacting a reference fluid with a specificity-determining substrate described in claim 1and an ambient fluid in a reference set of containers identical to the set used for the sample fluid, wherein the i-th container in the sample set and the i-th container in the reference set have the identical specificity-determining substrate and the identical ambient fluid conditions ($1 \leq i \leq N$) ;

d) identifying an n-th container in the sample fluid set whose amount of one or more proteins complexed with the substrate differs from the amount of the one or more proteins complexed with the substrate in the n-th container in the reference fluid set ($1 \leq n \leq N$); and

e) identifying the one or more proteins as the species whose amounts complexed with the substrate differ between the n-th sample container and the n-th reference container.